

## **EXHIBIT 5**

Entrez PubMed

Page 1 of 1



A service of the National Library of Medicine  
and the National Institutes of Health

My NCBI  
[Sign In] [Register]

All Databases	PubMed	Nucleotide	Protein	Genome	Structure	OMIM	PMC	Journals	Books
Search <input type="text" value="PubMed"/> <input type="button" value="Search"/>		for <input type="text"/>							
Limits <input type="button" value="▼"/>		Preview/Index <input type="button" value="▼"/>		History <input type="button" value="▼"/>		Clipboard <input type="button" value="▼"/>		Details <input type="button" value="▼"/>	
Display <input type="button" value="AbstractPlus"/>		Show <input type="button" value="20"/> <input type="button" value="▼"/>		Sort by <input type="button" value="▼"/>		Send to <input type="button" value="▼"/>			
<input type="button" value="Print"/> <input type="button" value="Email"/> <input type="button" value="Copy"/> <input type="button" value="Save"/> All: 1 Review: 0 <input type="button" value="▼"/>									

1: 1 Control Release. 2002 Feb 19;79(1-3):113-22.

[ELSEVIER] Links  
FULL-TEXT ARTICLE

**Percutaneous penetration and skin metabolism of ethylsalicylate-containing agent, TU-2100: in-vitro and in-vivo evaluation in guinea pigs.**

**Sintov AC, Behar-Canetti C, Friedman Y, Tamarkin D.**

Ben Gurion University of the Negev, The Institutes for Applied Research, 84105, Beer Sheva, Israel. [asintov@bgu-mail.bgu.ac.il](mailto:asintov@bgu-mail.bgu.ac.il)

The aim of this study was to investigate the percutaneous penetration and dermal metabolism of a new potential anti-acne prodrug--TU-2100 [bis(o-carboxyphenyl ethyl ester)nonanediolate] in guinea pigs. The fluxes of this agent through excised skin after applications of TU-2100 gels at 3 and 10% concentrations were similar. However, after 24 h from the time of drug application, the total amounts of permeated TU-2100 into the skin compartment and through the skin into the receiver were 271.7 (+/-30.7 S.E.) microg/cm<sup>2</sup> from the 3% gel and 779.4.0 (+/-98.5 S.E.) microg/cm<sup>2</sup> from the 10% gel, demonstrating a relatively high skin accumulation. Higher degradation of TU-2100 to ethylsalicylate occurred after application of drug at 10% concentration than after the application of 3% gel. In contrast, the fraction of permeated drug metabolized was twofold higher after the 3% gel application than after the 10% gel ( $F(m) = 20$  vs. 10.5 mole %). Since  $F(m)$  is reversibly related to the total permeating drug, the obtained values actually reflect the significant difference in TU-2100 permeation from the 3% (271.7 microg) and the 10% (779.4 microg) gels. An in vivo--in vitro comparison revealed similar drug accumulations in the skin after application of both 3 and 10% gels, however, skin metabolism was found to be significantly higher in vivo than in vitro.

PMID: 11853923 [PubMed - indexed for MEDLINE]

Display  Show   Sort by  Send to

[Write to the Help Desk](#)

[NCBI](#) | [NLM](#) | [NIH](#)

[Department of Health & Human Services](#)  
[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Aug 14 2006 08:07:58

Entrez PubMed

Page 1 of 2

**NCBI** **PubMed** [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov) A service of the National Library of Medicine and the National Institutes of Health

All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Books

Search  for

Limits Preview/Index History Clipboard Details

Display  AbstractPlus  Show 20  Sort by  Send to

All: 1 Review: 0

1: *Br J Dermatol* 2001 May;144(5):983-90.



Links

**A quantitative assessment of protoporphyrin IX metabolism and phototoxicity in human skin following dose-controlled delivery of the prodrugs 5-aminolaevulinic acid and 5-aminolaevulinic acid-n-pentylester.**

**Gerscher S, Connelly JP, Beijersbergen Van Henegouwen GM, MacRobert AJ, Watt P, Rhodes LE.**

Dermatology Unit, Department of Medicine, University of Liverpool, Liverpool, U.K.

**BACKGROUND:** Topical 5-aminolaevulinic acid (ALA) is widely used in photodynamic therapy (PDT) to generate protoporphyrin IX (PpIX) in the skin. However, other prodrugs may be more effective. **OBJECTIVES:** The pharmacokinetics of ALA- and ALA-n-pentylester-induced PpIX, together with the phototoxicity after PDT, were compared in human skin *in vivo*, using iontophoresis as a quantitative drug delivery system. **METHODS:** A series of six increasing doses of equimolar prodrug solutions was iontophoresed into normal skin of the upper inner arms of 20 healthy subjects. The kinetics of PpIX metabolism in skin ( $n = 4$ ) and the response to light exposure, performed at 4.5 h ( $n = 6$ ) and 6 h ( $n = 10$ ) after application, were assessed by skin surface PpIX fluorescence and postirradiation erythema. **RESULTS:** ALA and ALA-n-pentylester showed a linear correlation between logarithm of dose and PpIX fluorescence ( $P < 0.005$ ), and logarithm of dose and skin phototoxicity with irradiation at 4.5 h ( $P < 0.001$  and  $P < 0.005$ , respectively) and 6 h ( $P < 0.05$  and  $P < 0.0001$ , respectively) after iontophoresis. Higher phototoxicity was observed with ALA-n-pentylester than with ALA when sites were irradiated at 6 h, as indicated by the significantly lower theoretical threshold dose for erythema ( $P < 0.05$ ) and the shift of the PpIX fluorescence/phototoxicity curve towards greater skin erythema at equal PpIX fluorescence levels. Depth of PpIX fluorescence in skin, as determined by fluorescence microscopy, was similar for both prodrugs, but a more homogeneous distribution of PpIX was seen with the more lipophilic ALA-n-pentylester. **CONCLUSIONS:** The observed greater phototoxicity of ALA-n-pentylester relative to ALA may be attributable to a more favourable PpIX localization in tissue and/or greater intrinsic toxicity.

PMID: 11359385 [PubMed - indexed for MEDLINE]

Display  AbstractPlus  Show 20  Sort by  Send to

[Write to the Help Desk](#)  
NCBI | NLM | NIH

10/04/2006 17:04 +

REED SMITH 23MAILROM

PAGE 36/89

Entrez PubMed

Page 2 of 2

[Department of Health & Human Services](#)  
[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Aug 14 2006 08:07:58

**A. Maintenance Message**



# WILEY INTERSCIENCE

Home / Chemistry / Pharmaceutical and Medicinal Chemistry

**Medicinal Research Reviews**  
Volume 23, Issue 6  
Published Online: 20 Aug 2003  
Copyright © 2003 Wiley Periodicals, Inc.

[Save Title to My Profile](#)    [Set E-Mail Alert](#)

[Go to the homepage for this journal to access full sample issues, tables of contents, and recent information, news and more.](#)

[Save Article to My Profile](#)    [Download Citation](#)   [< Previous Abstract](#) | [Next Abstract >](#)

[Abstract](#) | [References](#) | [Full Text: PDF \(319k\)](#) | [Related Articles](#) | [Citation Tracking](#)

**Designing for topical delivery: Prodrugs can make the difference**  
Kenneth B. Sloan<sup>1</sup>, Scott Wasdo  
Department of Medicinal Chemistry, P.O. Box 100485, University of Florida, Gainesville, Florida 32610  
email: Kenneth B. Sloan ([sloan@cop.ufl.edu](mailto:sloan@cop.ufl.edu))  
\*Correspondence to Kenneth B. Sloan, Department of Medicinal Chemistry, P.O. Box 100485, University of Florida, Gainesville, FL 32610.

**Keywords**  
prodrugs • diffusion cell experiments • water solubility • lipid solubility • transformed Potts-Guy equation • series/parallel equation

**Abstract**  
It has been shown for homologous series of prodrugs that those members who were the more water soluble ones gave the greatest enhancement in topical delivery of the parent drug and not the more lipophilic ones. However, until recently models for topical delivery and equations to predict topical delivery focused only on lipid solubility ( $S_{LIPID}$ ) or partition coefficient ( $K_{OCT:AQ}$ ) and molecular volume (or molecular weight, MW) as parameters. Now several equations (transformed Potts-Guy or Series/Parallel) have been developed which include aqueous solubility ( $S_{AQ}$ ) as a parameter for predicting flux through skin. Experimental fluxes, solubilities, and MW from seven series of prodrugs have been fit to the transformed Potts-Guy equation to give coefficients for log solubility in isopropyl myristate (log  $S_{IPM}$ ) and log solubility in water (log  $S_{AQ}$ ) (0.53 and 0.47, respectively) which show, for parent drugs delivered by prodrugs from IPM *in vitro* through hairless mouse skin, that water solubility is almost as important as lipid solubility. When the transformed Potts-Guy equation was fit to data for the delivery of NSAID from mineral oil (MO) *in vivo* through human skin, the coefficients were 0.72 log  $S_{MO}$  and 0.28 log  $S_{AQ}$ . When the transformed Potts-Guy equation was fit to data for the delivery of their parent drugs by three series of prodrugs from water *in vitro* through hairless mouse skin the coefficients were 0.68 log  $S_{IPM}$  and 0.34 log  $S_{AQ}$ . Numerous recent examples are also given where more water-soluble members of homologous series of prodrugs give higher flux values from water vehicles *in vitro* through human skin than the more lipid soluble ones. © 2003 Wiley Periodicals, Inc. *Med Res Rev*, 23 No. 6, 763-793, 2003

**Digital Object Identifier (DOI)**  
10.1002/med.10048 [About DOI](#)

[My Profile](#) [Log In](#)

[HOME](#)  
 [ABOUT US](#)  
 [CONTACT US](#)  
 [HELP](#)

**SEARCH**  [All Content](#)  
 [Publication Titles](#)

[Advanced Search](#) [CrossRef / Google Search](#) [Acronym Finder](#)

**SEARCH IN THIS TITLE**  
Medicinal Research Reviews

[All Fields](#) [Go](#)

**SEARCH BY CITATION**  
Vol:  Issue:  Page:  [Go](#)

**LATEST IMPACT FACTOR**  
Medicinal Research Reviews   
The #1 Journal in Medicinal Chemistry with an Impact factor of 7.964!  
2005 ISI Journal Citation Report

**FEATURED ONLINE BOOKS**  
See OnlineBooks from Wiley InterScience in...

  
Pharmaceutical and Medicinal Chemistry [Go](#)

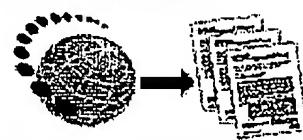
**Related Articles**

- Find other articles like this in Wiley InterScience
- Find articles in Wiley InterScience written by any of the authors

Wiley InterScience is a member of CrossRef.



**BEST AVAILABLE COPY**

**ARTICLE REPRINTS**

**Need an article reprint?**

Paper or electronic reprints are available for all articles published on Wiley InterScience. Inquiries can be submitted online.

[Find out more](#)

**COMING SOON**

**Pharmacology and Toxicology Backfile**  
(1822-2000)



Fully searchable and live-linked, the **Pharmacology and Toxicology Backfile Collection** brings the complete contents of 13 leading titles - 276,000 pages dating back to Volume 1, Issue 1 - to your desktop. A one-time fee delivers ongoing access with absolutely no strings attached.

[Request a Quote](#)

**NOW AVAILABLE**

**Evidence-Based Child Health:  
A Cochrane Review Journal**

A new online Cochrane review journal for all those involved in child health...

[Go to the journal](#)

**IN THE NEWS**

**Journal of  
Applied  
Toxicology**

Antiperspirants and cancer link?

Study of metalloestrogens provides clues for further research.

[View article abstract](#)

10/04/2006 17:04 +

REED SMITH 23MAILROM

PAGE 39/89

Wiley InterScience: Journal: Abstract

Page 3 of 3

[About Wiley InterScience](#) | [About Wiley](#) | [Privacy](#) | [Terms & Conditions](#)

[Copyright © 1999-2006 John Wiley & Sons, Inc.](#) All Rights Reserved.